

RECEIVED

PATENT COOPERATION TREATY

PCT

17 MAY 2005 INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

| CODE | DATE | NTD |
|------------------------|------|-----|
| | | |
| ANKOM 13 MAY 2005 GIPS | | |
| PRIORITY | | |
| ENTERED | | |
| FINAL CHECK 13 16/5/05 | | |

| | | |
|----------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|----------------------------------------------|
| Applicant's or agent's file reference 100931-1 WO | FOR FURTHER ACTION See Form PCT/IPEA/416 | |
| International application No. PCT/SE2004/000227 | International filing date (day/month/year) 19.02.2004 | Priority date (day/month/year) 21.02.2003 |
| International Patent Classification (IPC) or national classification and IPC C07C 13/615, A61P 37/00, A61P 29/00, A61K 31/166 | | |
| Applicant AstraZeneca AB et al | | |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
 - a. ☐ (sent to the applicant and to the International Bureau) a total of _____ sheets, as follows:
 - ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
 - ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
 - b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- | | |
|-------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input checked="" type="checkbox"/> Box No. I | Basis of the report |
| <input type="checkbox"/> Box No. II | Priority |
| <input checked="" type="checkbox"/> Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input type="checkbox"/> Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input type="checkbox"/> Box No. VI | Certain documents cited |
| <input type="checkbox"/> Box No. VII | Certain defects in the international application |
| <input type="checkbox"/> Box No. VIII | Certain observations on the international application |

| | |
|-----------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Date of submission of the demand 06.09.2004 | Date of completion of this report 25.04.2005 |
| Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. +46 8 667 72 88 | Authorized officer Johanna Brolund / MRO Telephone No. +46 8 782 25 00 |

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/SE2004/000227

Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

- ☐ international search (under Rules 12.3 and 23.1(b))
☐ publication of the international application (under Rule 12.4)
☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☒ the international application as originally filed/furnished

☐ the description:

pages _____ as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ the claims:

pages _____ as originally filed/furnished

pages* _____ as amended (together with any statement) under Article 19

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ the drawings:

pages _____ as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing (*specify*): _____

☐ any table(s) related to the sequence listing (*specify*): _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing (*specify*): _____

☐ any table(s) related to the sequence listing (*specify*): _____

* If item 4 applies, some or all of those sheets may be marked "superseded."

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/SE2004/000227

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application☒ claims Nos. 19-20

because:

☒ the said international application, or the said claims Nos. 19-20
relate to the following subject matter which does not require an international preliminary examination (*specify*):

Claims 19-20 relate to methods of treatment of the human or animal body by surgery or by therapy. See PCT Rule 67.1.(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.☐ no international search report has been established for said claims Nos. _____☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the
Administrative Instructions in that:

the written form

☐ has not been furnished☐ does not comply with the standard

the computer readable form

☐ has not been furnished☐ does not comply with the standard☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with
the technical requirements provided for in the Annex C-bis of the Administrative Instructions.☐ See Supplemental Box for further details.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/SE2004/000227

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. Statement**

| | | | |
|-------------------------------|--------|-------------|-----|
| Novelty (N) | Claims | <u>1-18</u> | YES |
| | Claims | | NO |
| Inventive step (IS) | Claims | | YES |
| | Claims | <u>1-18</u> | NO |
| Industrial applicability (IA) | Claims | <u>1-18</u> | YES |
| | Claims | | NO |

2. Citations and explanations (Rule 70.7)

The following documents are cited in the International Search Report:

D1: US 2003/0013704 A1
D2: US 6492355 B1
D3: US 2001/0003121 A1
D4: US 6201024 B1
D5: US 6242470 B1

The present application relates to adamantane derivatives of formula (I), processes for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions and their use in therapy. The problem solved by the present application according to claims 1-18 is to provide compounds effective as P2X₇-receptor antagonists for use in the treatment of inflammatory, immune or cardiovascular diseases.

D1, which represents the closest prior art, discloses adamantane derivatives, their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions and their use in therapy. The adamantane derivatives are used as P2X₇-receptor antagonists i.e. in the treatment of inflammatory diseases.

.../...

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: BOX V

Claim 1 of the present application differs from D1 in that the hydroxyl group close to the amine group in claim 1 is absent in the structure of D1 (page 1, passages [0008]-[0009], R⁴). The compounds are structurally similar and have similar effect (examples 3-4, 6-7 11-12 and 14; page 6 passage [0146] and page 33 passage [0543] of D1). The problem to be solved by the present invention may therefore be regarded as finding new compounds for use in medicaments for the treatment of the diseases mentioned in the application. It is considered obvious for a person skilled in the art with knowledge of D1 to place a hydroxyl group at this position. Thus, claim 1 lacks inventive step.

Documents D2-D5 show similar compounds having the same field of application.

In order to justify the patentability of the present subject-matter, the technical effect of the claimed compounds must be shown. This can, for example, be done by comparative experiments, showing that the compounds according to the claim(s) have such unexpected and beneficial effects, compared to the previously known similar compounds, that they can be considered to differ essentially from said compounds. In order for a compound to be considered patentable, this difference must be shown to result in a novel and unexpected technical effect. The applicant has not indicated any difference in relation to prior art and the significance of such a difference for the whole of the scope of the claims.

The compounds, products and processes claimed in dependent claims 2-18 do not differ significantly from what is previously known from the cited documents. Thus, these claims lack inventive step.